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Multiple sclerosis in the Orkney and Shetland Islands

I: Epidemiology, clinical factors, and methodology

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SUMMARY An epidemiological and clinical study of multiple sclerosis (MS) in the Orkney and Shetland Islands showed that the prevalence rate of the disease is the highest in the world (309 and 184/100 000, respectively). The clinical entity, MS, is similar to that found in other parts of the world, except that optic neuritis *not* followed by MS is rare. Analysis of death certificates indicated that MS has probably occurred at the same rate in these islands for nearly a century. Although the incidence of MS is high, the incidence rate has remained constant over time. A rapidly increasing prevalence of MS has occurred in Orkney, with a more modest increase in Shetland, over the past 20 years, which is largely due to an increase in survival. Demographic factors, case ascertainment, and emigration have contributed little to the increasing prevalence of MS in these islands.

Beginning seven miles north of the northernmost point in Scotland and extending 50 miles north northeastward lie the Orkney Islands, a group of about 70 islands, islets, and skerries, of which 26 are inhabitated (Fig. 1). The area of the Orkneys is 376 square miles with a population in 1971 of 17 077. Orkney's largest island is the Mainland with an area of 207 square miles, containing the two burghs Kirkwall and Stromness that comprised about one-third of the total population in 1971. Approximately 70% of the population live on the Mainland.

The Shetland Islands, which lie an additional 40 miles north northeastward at a latitude 60° to 61° north, are a group of more than 100 islands, with the capital at Lerwick, 300 miles north by east of Edinburgh and 220 miles west of Bergen, Norway (Fig. 2). Lerwick comprised 40% of Shetland's total

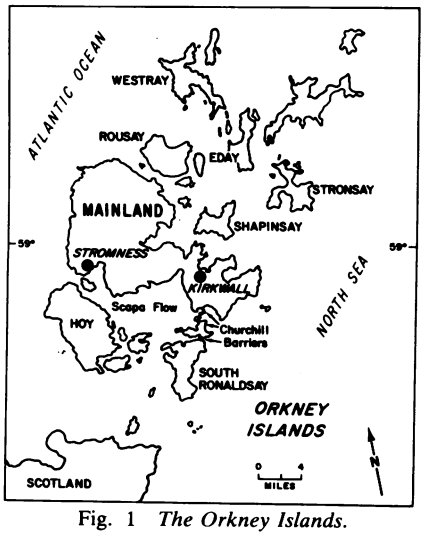

Fig. 1 *The Orkney Islands.*

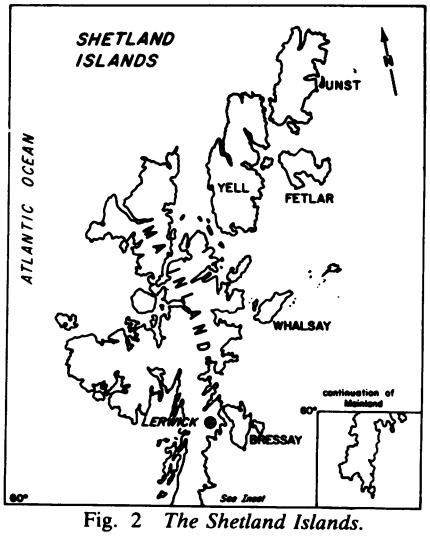

Fig. 2 *The Shetland Islands.*

population in 1971. Kirkwall in Orkney and Lerwick in Shetland are 100 miles apart. The total area of the Shetlands is 550 square miles with a population in 1971 of 17 327. There are 19 inhabitated islands, including the Mainland with 378 square miles and 80% of the total population in 1971.

On each island, there is a small hospital for acute medical care, a small chronic disease hospital, and one active surgical consultant. Nineteen general practitioners (GPs) provide medical care in Orkney; in Shetland there are 13. Aberdeen is the referral centre; consultants visit the islands regularly.

Sutherland first demonstrated that the prevalence of multiple sclerosis (MS) was about twice as high in the Shetland and Orkney region as in the Highland areas of Scotland.[1] He drew attention particularly to the counties of Shetland, Orkney, and Caithness, the northernmost Scottish mainland county. At the time when his paper was published, in 1956, only a handful of prevalence studies of MS had been carried out, and the pattern of geographical distribution was not clearly defined. Only later did it become apparent that the areas pointed to by Sutherland had not only a high rate of MS but in fact the highest prevalence of any competently surveyed area in the world.

In 1962, Allison and Fog and Hyllested undertook a study of the occurrence of MS in the Orkney, Shetland, and Faroe Islands and found the prevalence of the disease in the Orkneys and Shetlands to be almost three times that recorded anywhere else in the world.[2,3]

In 1970, Poskanzer, Brody, and Plank visited the Shetland and Orkney Islands.[4] Their investigation was intended to confirm the high rate of prevalence previously recorded and to ascertain whether a continued high incidence of MS was present. It was hypothesised that perhaps those individuals who were well and able to emigrate had left the islands, leaving behind a much higher proportion of those incapacitated by neurologic illness. In the third survey, all new patients reported since 1962 were examined, based on the evaluations of Allison, Fog, and Hyllested, and patients previously diagnosed as possible or doubtful in 1962 were re-evaluated.

Methods

In the investigation repeated here, an extensive epidemiologic, virologic, and genetic study of MS was undertaken from 1974 to 1977 in the Shetland and Orkney Islands. Each case was reviewed and evaluated by a single individual (DCP) and classified as probable, possible, or not MS according to the criteria of Allison and Millar.[5] Patients with clear-cut clinical evidence of MS indicated by more than one lesion of the central nervous system and a clear history of exacerbations and remissions were diagnosed as probable. Documentation of cerebrospinal fluid abnormalities, when available, was confirmatory but not essential. Patients who had signs and symptoms indicative of MS that failed to meet the above criteria or who were not personally examined were diagnosed as possible.

The names of patients with MS were obtained from the GPs, public health nurses, and officials of the local MS societies in the two islands. For each patient, two controls who did not have neurological disease and who were unrelated to the patient were selected. The first one, designated a parish control, was an individual who was born in the same parish and year as the patient and was of the same sex. A sample frame of 10 names (births on each side of the patient's) was derived for each patient from registers of birth located at the office in Edinburgh of the Registrar General for Scotland. No more than one year in either direction from the patient's date of birth was required to draw up a suitable sample frame. The names in the sample frame were placed in random order and intensive efforts were made to locate the first individual on the list. When all efforts to find the individual failed, the process was repeated with the subsequent names on the list until a control was found. The mean number of names utilised from the sample frames to find a parish control resident in Orkney and Shetland and willing to participate in the study was 2·5.

Because of the possibility that parish controls, by sharing a parish environment similar to that of the patients, might be overmatched for some aetiological factor, a second control was chosen. This control, designated a discontiguous control, was chosen by weighting all parishes by population in each set of islands in the census year closest to year of birth of the patient. A random number was then chosen and applied to the weighted alphabetical list of the parishes. If the initial parish selected was adjacent to that of the patient, it was discarded and a second random number was chosen and the procedure repeated until a discontiguous parish was selected. In only three instances was it necessary to repeat the random selection of parishes to find one not encroaching upon that of the patient. After selection of the discontiguous parish, the 10 births of the same sex closest to the patient's were selected, and this grouping constituted the discontiguous control panel. A mean number of 3·1 names was required to find a suitable discontiguous control from the panels of 10 randomly listed individuals. Five patients were not born in Orkney and Shetland, and no controls were chosen for them.

The most common reasons for the failure to find an individual from any given sample was emigration or

death. Both patterns were more marked among the older patients. Only two individuals selected as controls refused to participate in the study. In three instances, controls were found to have neurologic diseases by examination or history which disqualified them as controls.

Results

CLINICAL STUDIES

The clinical disease, MS, in the Orkney and Shetland Islands differed very little from that encountered in other parts of the world (the counties of Northumberland and Durham in England; Australia; and Massachusetts).[6–8] Classification by first symptom, by degree of disability, and by clinical course, although admittedly gross and difficult, failed to disclose important differences except as noted below.

Permission to examine and interview five patients was denied by their GPs; one patient refused to participate in the study. These patients were assigned to the 'possible' category, despite adequate histories which were made available confirming their diagnosis. Close correlation existed between diagnoses in the patients evaluated originally by Sutherland,[1] Allison,[2] or Fog and Hyllested[3] and evaluated again in the present study. Table 1 indicates patient status by the categories probable, possible, or not MS.

Table 1 *Diagnosis of multiple sclerosis (MS) in the Orkney and Shetland Islands, 1974-1975*

	*Orkney**	*Shetland*
Patients examined for neurological disease	62	60
Probable MS	47	28
Possible MS	10	6
Possible MS Diagnosis by record review, not personally examined	5	1
Optic neuritis only	0	2
Patients with diagnosis other than MS	9	18

* Three patients in Orkney came to our attention after prevalence day (1 December 1974) and were not included in calculation of prevalence rate.

The age of onset of the disease in the two areas differed significantly. In Orkney, the mean age at onset was 33·6 years and in Shetland 29·0 years. In Shetland, 60% of the patients had onset before the age of 30.

Diagnosis was generally more difficult in a greater number of patients in Shetland than in Orkney, but this may reflect the availability of medical records, the frequency of referrals to consultants who provided additional historical information obtained early in the course of illness, and the frequency with which patients were sent to Aberdeen for inpatient hospital study. Remarkably, 17% of the cases in Orkney and 18% in Shetland were recorded as possible. More cases were discarded as not MS in Shetland than in Orkney.

Despite re-evaluation of cases over time, which allowed cases listed as possible in a previous evaluation to be either designated probable or discarded, a significant number of cases remained in the possible category and these cases were not necessarily those with recent onset. Over the period of the four studies the length of time from onset to diagnosis has decreased only slightly, from 7·5 years to 5·2 years. The re-evaluation of cases over time improves case definition but apparently does not shorten the interval required for a patient to have two clearly defined episodes in more than one location of the central nervous system.

TEMPORAL COURSE

A classification of the temporal course of MS in these patients, as shown in Table 2, demonstrated that over 50% of patients in this investigation had the classical remitting-relapsing form of the disease. As has been noted in other studies, male patients tended to have the chronic progressive form of the disease in our series, while female patients more commonly exhibited the relapsing-remitting form.[9] Thirty-four (71%) of those with the remitting-relapsing course were female patients; only five per cent of female patients had the chronic progressive form of the illness, compared with 18% of male patients. A difference in age at onset of MS was observed for those patients with the relapsing-remitting course as contrasted with the chronic progressive course; 28·8 and 35·6 years respectively. This observation is consistent with other studies that demonstrate a later onset in those cases which are progressive from onset.[9]

Table 2 *Temporal course of multiple sclerosis in the Orkney and Shetland Islands*

	No. of patients		
	Orkney	*Shetland*	*Total*
Relapsing-remitting	29	19	48
Relapsing-remitting leading to chronic progressive	14	4	18
Chronic progressive with exacerbations and no remissions	5	10	15
No clear-cut exacerbations, chronic progressive	4	0	4
Unclassified and insufficient information	5	1	6
TOTAL	57	34	91

It is tempting, from an epidemiological point of view, to regard these consistently observed features as manifesting two variants of the same disease, one marked by a young age at onset of the relapsing-remitting form with an excess in females, the other characterised by an older age at onset of the progressive form seen more commonly in males. It is widely believed that the course of the disease is influenced by age at onset. Just as striking in this series was the frequency with which the relapsing-remitting form of the disease occurred in females.

SYMPTOMS AT ONSET

Over 50% of the patients in the Orkney and Shetland series had an initial symptom referable to the spinal cord, as shown in Table 3. Motor weakness was the most prominent symptom, followed by sensory disturbances, motor and sensory symptoms combined, and bladder dysfunction. Optic neuritis alone or in combination with other symptoms was observed in 15% of patients. Seventy per cent of patients were monosymptomatic at onset.

Table 3 *Initial symptoms in patients with multiple sclerosis in the Orkney and Shetland Islands*

	Orkney Islands		*Shetland Islands*	
Symptom	*No.*	*%*	*No.*	*%*
Spinal cord (total)	30	53	19	56
Motor	13	23	12	35
Sensory	11	19	7	21
Mixed	5	9	0	0
Bladder	1	2	0	0
Brain stem and cerebellar	13	23	7	21
Optic neuritis	7	12	3	9
Multiple lesions	7	12	4	12
Other	0	0	1	3
TOTAL	57		34	

OPTIC NEURITIS

The only important clinical difference between the MS patients in these islands and those studied elsewhere was a paucity of cases of optic neuritis which were *not* followed by MS. Depending on the study and the length of follow-up, between 11·5% and 78% of optic neuritis patients (the lower figures are often found in the more reliable studies) over many years develop full-blown MS.[10 11] It is not clear whether optic neuritis alone represents a *forme fruste* of the disease or whether there is another aetiology for optic neuritis. Only two patients with optic neuritis were discovered in the two island groups; one had bilateral optic neuritis at different times and the other had a single episode with no other symptoms. Optic neuritis as an isolated entity without subsequent development of MS appears to be a rare event in these islands.

The islands are visited regularly by an ophthalmological consultant who reported that he had rarely, if ever, seen optic neuritis as a discrete entity during 20 years of visiting the islands. Despite a search of hospital records for ophthalmological consultations and discussion with the optometrists and the GPs in both islands, no additional cases were found of optic neuritis unassociated with other signs of MS. Because loss of vision in one eye is such a disturbing handicap, it seems unlikely that such cases would not have come to the attention of the two optometrists, the GPs, or the consultants. This finding may suggest that MS, when it occurs in these islands, is more severe than in other areas. However, this conclusion is not borne out by the degree of disability observed in these patients compared with those seen elsewhere.

Optic neuritis alone as a presenting symptom was observed in 11% of all patients; a similar finding has been reported in other studies.[9 12] The mean duration from onset of optic neuritis to the subsequent development of MS in these patients was 9·2 years, and their mean age at onset was 23·9 years. The latter figure is lower than that reported by Leibowitz and Alter[9] who found a mean age at onset of 28·8 years in patients with optic neuritis as a first symptom.

HISTORY OF MS IN THE ORKNEY AND SHETLAND ISLANDS

Although the first pathological descriptions of MS were published by Cruveilhier in 1835 and Carswell in 1838,[13] it was not until 1872 that Charcot provided the first extensive clinical description of the disease.[14] The first clinical case of MS in England was reported by Moxon in 1873.[15]

Death certificates at Register House in Edinburgh were reviewed for deaths ascribed to neurological disease in Orkney and Shetland for a random sample of 16 years for the period 1880–1912. All deaths in Orkney and Shetland are recorded by parish, and copies of the death certificates are sent to the Registrar General in Edinburgh. Death certificates record the diagnosis, age at death, length of illness, occupation, and residence of the deceased.

This review was undertaken to ascertain the nature and frequency of deaths that could reasonably be ascribed to MS. Cases were categorised as (1) 'Disseminated sclerosis' where so stated; (2) Possible MS; (3) MS not likely; or (4) Other neurological disease (Table 4).

The first recorded diagnosis of disseminated sclerosis occurred in an Orcadian who died in 1898. Ten years later, a second case was recorded. After that, the diagnosis appeared routinely. Clinical

Table 4 *Review of death certificates with diagnoses of neurological disease in the Orkney and Shetland Islands, covering 16 random years in the period from 1880 to 1912**

No. of cases a year	*CATEGORIES*			
	Disseminated sclerosis (MS)	*Possible MS*	*Not likely MS*	*Other neurological disease*
Orkney	7	19	18	34
Shetland	3	23	17	25
Total	10	42	35	59

* Based on death certificates filed at Register House, Edinburgh.

diagnosis can be assumed to have preceded death certificate diagnosis, perhaps by some years. Physicians in north-east Scotland began using the diagnosis of disseminated sclerosis in the late 1880s.[16]

The classification of neurological disease not diagnosed as disseminated sclerosis on death certificates before 1908 was difficult. Attention was paid not only to the diagnosis but to the age at death and length of illness. Diagnoses such as 'chronic paralysis' and 'paraplegia' without mention of antecedent trauma in persons under 50 were classified as possible MS. Although the Wasserman test did not come into general use until 1908, it is believed that the experienced practitioners in these islands made relatively reliable diagnoses of the two common central nervous system manifestations of tertiary syphilis—tabes dorsalis (referred to as 'locomotor ataxia' and 'spinal sclerosis') and paresis (termed 'general paresis', or 'general paresis of the insane'). In our classification, these diagnoses were categorised as other neurological diseases. The diagnosis of the hereditary spinocerebellar degenerations such as Friedreich's ataxia was rare in the islands on clinical review.

Although it was difficult to estimate the frequency of MS before 1912 based on death certificate information, the data suggest that MS may have been as frequent then as it is now (Table 5). The number of death certificates indicating a diagnosis of disseminated sclerosis or judged to be possible MS was 1·6 a year over the 16 sample years for which all death certificates were surveyed in Orkney and Shetland. That rate is comparable to the one calculated for 1957 to 1974, based on death certificates filed in this period (1·7 deaths a year in Orkney and 1·4 deaths a year in Shetland).

PREVALENCE, INCIDENCE, AND DURATION

Prevalence

Four surveys carried out in 1954,[1] 1962,[2 3] 1970,[4] and 1974[17] showed that the prevalence of MS has risen dramatically in the Orkney Islands; during the same

Table 5 *Review of death certificates with diagnoses of neurological disease in the Orkney and Shetland Islands by year, for 16 randomly selected years during the period 1880 to 1912**

Year of death	*CATEGORIES*			
	Disseminated sclerosis (MS)	*Possible MS*	*Not likely MS*	*Other neurological disease*
1880	—	3	4	2
1885	—	1	3	8
1888	—	3	2	4
1890	—	4	1	4
1893	—	—	2	3
1895	—	2	1	8
1896	—	—	1	1
1897	—	1	4	1
1898	1	5	3	7
1900	—	8	6	10
1902	—	4	3	2
1905	—	2	—	5
1908	5	—	—	1
1909	1	2	1	—
1910	2	5	2	1
1912	1	2	2	2
TOTAL	10	42	35	59

* Based on death certificates filed at Register House, Edinburgh.

Table 6 *Multiple sclerosis in the Orkney Islands: four surveys over 20 years*

Survey	*1954*	*1962*	*1970*	*1974*
Prevalence day	31 May	1 December	15 August	1 December
Probable MS cases	17	31	38	45
Possible MS cases	6	2	2	9
Total cases (probable and possible)	23	33	40	54
Population	20 746	18 531	17 077	17 462
Prevalence rate/100 000 (probable and possible)	111	178	234	309
Prevalence rate/100 000 (probable)	82	167	223	258

Table 7 *Multiple sclerosis in the Shetland Islands: four surveys over 20 years*

Survey	*1954*	*1962*	*1970*	*1974*
Prevalence day	31 May	1 December	15 August	1 December
Probable MS cases	22	21	23	28
Possible MS cases	3	8	8	6
Total cases (probable and possible)	25	29	31	34
Population	18 715	17 537	17 327	18 445
Prevalence rate/100 000 (probable and possible)	134	165	179	184
Prevalence rate/100 000 (probable)	118	120	133	152

period there was only a slight, non-significant increase in the Shetland Islands (Tables 6 and 7). Increased prevalence over time may be due to any combination of five factors: (1) an increase in the incidence of the disease; (2) an increase in survival (duration of the disease); (3) more complete ascertainment of cases upon restudy; (4) changes in the age structure of the population; or (5) differential migration of patients compared with the general population.

Major sources of error in determining the incidence and duration of MS in a point survey include incomplete ascertainment of cases with onset too recent to have reached diagnosis and failure to record cases who have emigrated or died. Additional error stems from lack of precision in establishing the onset of disease. Initial attacks may be transient and mild and in many cases leave no permanent deficit. A decade or more may elapse from initial symptom to diagnosis by a physician. In the interim, there may be memory loss or selective recall or more dramatic symptoms such as visual loss compared to paresthesiae in an extremity.

Incidence

Changes in the incidence of a disease may reflect alterations in environmental exposures, while unaltered incidence may permit the exclusion from aetiologic consideration of factors that have undergone change, such as immunisation policy.

The years of onset for all probable cases of MS in Orkney and Shetland derived from the four investigations are presented in Figs. 3 and 4. The studies identified 66 probable cases in Orkney and 53 in Shetland with a known date of onset. Firm dates of onset could not be determined for two Orcadians and one Shetlander. From 1930 to 1969, a period during which most of the cases had onset, the average number of new cases a year in Orkney was 1·6 and in Shetland 1·3. In both islands the incidence was

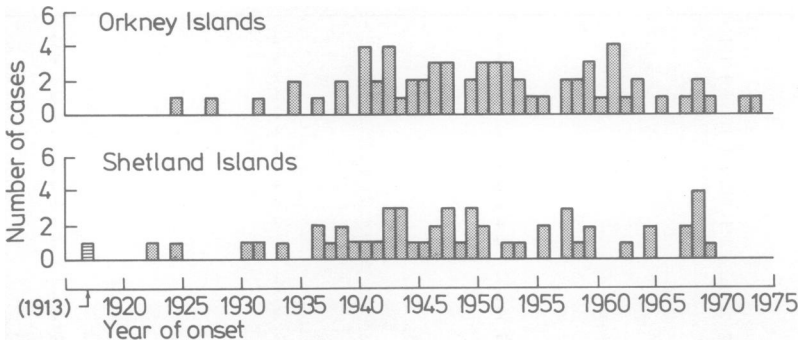

Fig. 3 *Year of onset of probable multiple sclerosis cases identified in four surveys.*

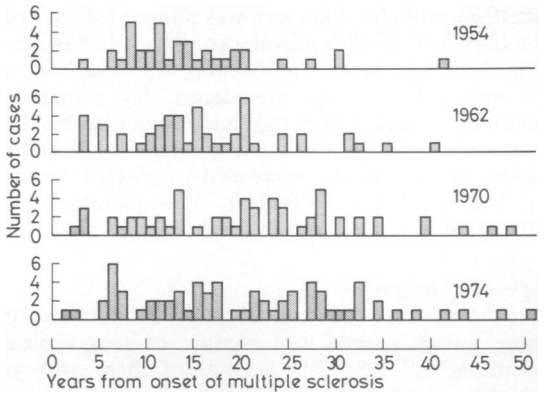

Fig. 4 *Interval (years) from onset of multiple sclerosis to prevalence year. Probable patients in each of four surveys, Orkney and Shetland Islands.*

relatively constant. Incomplete ascertainment of MS cases because of death or emigration is evident at one end of the distribution. The paucity of cases at the other end represents cases that have not yet been diagnosed. The distributions level out between 1940 and 1960, a period during which ascertainment would be most complete. At that time, there was an annual average of 2·2 cases in Orkney and 1·6 cases in Shetland with onset of MS.

Annual incidence rates were calculated for five-year periods from 1940 to 1969 (Table 8). The rates were relatively constant over the 30-year period, averaging 9·3/100 000 in Orkney and 7·5/100 000 in Shetland. The rates appear to drop off slightly in the later years because of incomplete ascertainment of undiagnosed cases. This result is slightly accentuated by the exclusion from rate calculation of 'possible' cases identified in the 1974 survey, many of whom had onset of disease a few years before prevalence day (1 December 1974). Experience indicates that in time many of these possible cases will be reassigned to the 'probable' category.

Death certificates, although much less reliable than case survey data, lend further support to the evidence that shows an unchanging incidence. In the 25-year period from 1950 to 1974, 43 MS deaths were recorded in Orkney and 35 in Shetland, or 1·7 deaths a year in Orkney and 1·4 a year in Shetland, remarkably similar to the number of new cases a year discussed above. Deaths were evenly distributed over the 25-year period and were probably well reported in this area of high recognition for MS.

The incidence and crude death rates in these islands are two to four times greater than those reported in other geographical areas and are consistent with the high prevalence rates found in the islands.[17] The unchanging incidence rate demonstrated in this study is in agreement with other long-term or repeated studies (Rochester, Minnesota; New Orleans; Winnipeg; and Northern Ireland).[18–21] The studies in Rochester are unique in that both prevalence and incidence data are available for a 60-year period.[18] Prevalence increased steadily from 46/100 000 in 1905–14 to 88/100 000 in 1955–64. Over this same period the incidence of the disease remained relatively constant, averaging 3·6/100 000 cases a year.[18]

Duration

True ascertainment of duration of a disease requires delay until all patients in the observed cohort are dead. Because duration affects prevalence

Table 8 *Annual incidence rates of multiple sclerosis based upon year of onset of probable cases identified in the four surveys*

	SHETLAND			*ORKNEY*		
	No. of cases	*Island population*	*Incidence (per100 000/yr)*	*No. of cases*	*Island population*	*Incidence (per 100 000/yr)*
Before 1940	12			8		
1940–44	9	19 868[1]	9·1	13	21 641[1]	12·0
1945–49	10	19 352[2]	11·4	10	21 255[2]	9·4
1950–54	4	19 352[2]	4·1	12	21 255[2]	11·3
1955–59	8	17 812[3]	9·0	8	18 747[3]	8·5
1960–64	3	17 812[3]	3·4	8	18 747[3]	8·5
1965–69	7	17 327[4]	8·1	5	17 077[4]	5·9
1970–prevalence day	0			2		
Average annual incidence of MS over 30-year period (1940–69)			7·5			9·3
Total no. of probable cases	53			66		

[1] Based upon 1939 mid-year census estimate (no 1941 census).
[2] Based upon 1951 census.
[3] Based upon 1961 census.
[4] Based upon 1971 census.

(prevalence = incidence × duration) such changes may be important. Estimates of the average duration of MS summarised by Leibowitz and Alter range from 9·2 to 25 or more years.[9] In early studies of hospital and clinic patients estimates of survival were low.[22–25] More recent epidemiological studies have achieved better ascertainment of cases in defined populations and estimates of survival have been appreciably more optimistic.[6 18 26 27] For example, the study of MS in Rochester, Minnesota, found that 74% of patients survived for 25 years after onset, compared with 86% of the normal population.[18] Two-thirds of the survivors were still ambulatory after 25 years, suggesting more complete ascertainment of benign cases normally excluded from hospital and clinic-based studies.[18] The highest estimate of mean duration, 35 years, was reported in a follow-up study among military servicemen.[27]

Deceased patients in the Orkney and Shetland Islands who were included in at least one of the four surveys had a mean duration of the disease of 22 years and 27 years respectively. This group must necessarily include early deaths; therefore, the duration of the disease for the total patient population is probably greater.

An indirect method for determining duration was proposed by Poskanzer *et al.*[6] Assuming that there is no change in the pattern of a disease, average duration can be estimated as twice the period from onset to prevalence day. It is further assumed that the duration among a group of patients identified on prevalence day will approximate to a normal distribution and that ascertainment of nearly all existing cases will be achieved, especially those cases with recent onset of the disease. The latter requirement has probably not been fully met in each of the four surveys in the islands. However, the method can be applied by using information discovered later about cases with onset close to prevalence day. The effect of not identifying all cases with recent onset overestimates the average duration. If it is assumed, however, that the error resulting from the exclusion of recent onset cases is relatively constant over the four surveys, the data can be used to determine if the duration has changed over time but *not* to determine the actual duration of the disease.*

The median interval from onset to prevalence day was calculated for probable cases in Orkney and in Shetland for each of the four surveys. Duration increased 54% (26 years to 40 years) in Orkney and 42% (24 years to 34 years) in Shetland from the 1954 to the 1974 study. The year of onset for Orkney and Shetland probable MS cases was plotted for each of the four surveys with prevalence years as a baseline (Fig. 4). While the number of cases with onset within 10 and 20 years of prevalence day remained relatively constant over the four investigations, the proportion of cases with onset greater than 20 years before prevalence day increased steadily over time ($\chi^2 = 23{\cdot}6$, 3 df, $P < 0{\cdot}001$). This increase was attributed to an increase in survival (duration).

Effects of re-study

The prevalence of MS has been calculated for two or more points in time in a number of geographical locations.[1–3 17 19 20 26 28–33] Several of these surveys have shown substantial increases in prevalence from the earlier to the later study.[1–3 17 26 30–32] In others, prevalence has remained essentially unchanged.[6 19 20 28 29] Studies in which an increase in prevalence has been pronounced probably reflect increased survival, while effect of re-study has been minimal. For example, studies in Denmark and Switzerland demonstrated that prevalence more than doubled between the first and second surveys, which were separated in each country by more than 20 years.[26 30–32] Repeated surveys, resulting in better ascertainment of cases, have less of an effect on prevalence as the time between the two surveys increases. Even re-surveys at short intervals are less likely to be affected by changes in duration of disease. In repeat studies done at short intervals, alterations in prevalence have not been large.[6 19 20 29 33]

Because the Orkney and Shetland Islands have been studied four times in 20 years, the earlier surveys have influenced subsequent case ascertainment. A measure of the degree of case ascertainment in the earlier studies is provided by examining year of onset and year of diagnosis for new identified patients in each subsequent survey (Table 9). In toto, 14 probable cases in Shetland and 26 in Orkney were identified who had onset before 1954 but were not included in the 1954 study. The majority of these cases were diagnosed after the 1954 study had been completed. In the 1962 survey, there were 15 probable cases in Orkney and six in Shetland with onset before 1962 who were identified in the 1970 or 1974 surveys, but only three cases had been diagnosed before 1962. Case ascertainment in the 1970 study cannot be adequately measured because of the short time interval between it and the subsequent study (1974). Five cases who had onset between 1962 and 1970 were newly identified in the 1974 survey, but all were diagnosed after 1970.

The increase in prevalence of MS in these islands over the four investigations can in part be explained by more complete case ascertainment because of re-study. Because the prevalence rate in the 1954

* See discussion below on the effects of restudy. Case ascertainment was least complete in the earliest (1954) survey. Consequently, there was a greater overestimation of duration at that time.

Table 9 *Prevalence rates for multiple sclerosis in the Orkney and Shetland Islands corrected for additional cases discovered later and for emigration and differential emigration by applying cases to the 1954 population*

Survey	*Probable cases*	*Population*	*Prevalence rate/ 100 000*	*Additional probable cases found later*	*Prevalence rate/ 100 000*	*Prevalence rate based on additional cases and 1954 population (20 746)*
ORKNEY						
1954	17	20 746	82	26	207	207
1962	31	18 531	167	15	248	222
1970	38	17 077	223	5	252	207
1974	45	17 462	258	—	—	—
SHETLAND						1954 population (18 715)
1954	22	18 715	118	14	192	192
1962	21	17 537	120	6	154	144
1970	23	17 327	133	5	162	150
1974	28	18 445	152	—	—	—

study is understated, the rates in the subsequent surveys, each building on the one before, appear larger by comparison.

AGE STRUCTURE AND MIGRATION

Changes in the age structure of the population do not influence the prevalence of a relatively uncommon disease unless these changes are marked.[34] When the numerator is small compared with the denominator, a large change in denominator is required to alter the rate substantially. In most prevalence studies, the rates of MS have peaked in the fifth decade of life.[35] An aging population would therefore tend to increase the prevalence of the disease. Depopulation of the Orkney and Shetland Islands by the young has resulted in weighting of the population toward the older age groups.[36] Census reports reveal that the age group 50–69 is the only one that has increased in proportion to the population in the past 20 years.* The aging of the population from 1951 to 1971 has had a minimal effect on prevalence, which has increased 200% in Orkney and 29% in Shetland during this period.

The relationship of demographic movement to MS in the Orkney and Shetland Islands has been examined by Taylor *et al.*[34] They conclude that the extremely high prevalence in these islands is only partially accounted for by demographic factors and they suggest that the high rates represent an increased frequency of MS. Not only does emigration affect the denominator but differential migration of well persons, leaving patients with MS behind, might alter the rates. Because few official data on migration are available, population censuses have been used.[37–40] Between 1924 and 1974, there was little immigration to these islands; therefore, changes in population distribution reflect outmigration and alterations in patterns of fertility. The populations of Orkney and Shetland were at their highest levels in about 1861 and have since declined, with losses averaging 6% a decade, as the result of economic and social changes. Between 1939 and 1951, the population loss in both islands was relatively low (2%) but from 1951 to 1961 the population decreased by 12% in Orkney and 8% in Shetland. There was an influx of service personnel in bases like Scapa Flow during the second world war, and the attendant high employment explains the slow decline of population in the years 1939–51. Economic difficulties throughout Scotland, but particularly in the islands, contributed to emigration thereafter.

An estimate of the effect of restudy on case ascertainment and of differential emigration of well individuals was made in the 'worst case' by correcting the prevalence rates in the four studies for all cases known to exist at the time but not ascertained. Rates were recalculated using the population figures of 1951—the largest population before decline due to emigration (Table 9). This correction assumes that cases did not emigrate while well individuals did. With these two corrections, the prevalence rates in both Orkney and Shetland are unchanging, but no allowance is made in this calculation for cases not yet ascertained.

Conclusions

Clinical MS in the Orkney and Shetland Islands appears to be similar to that found in other parts of the world, except that optic neuritis *not* followed by MS occurs with considerably less frequency than in other studies. The age of onset of the disease was somewhat later in Orkney than in Shetland patients (33·6 compared with 29·0 years). The rate of possible cases was remarkably similar in the two islands (17% and 18%). Despite study of the population at four points in time over a period of 20

* In Orkney, the proportion of the population aged 50–69 increased from 20·4% in 1951 to 25·6% in 1971. In Shetland, the increase was more modest, from 22·7% in 1951 to 25·3% in 1961, followed by a slight decrease in 1971 to 23·6%.

years, the mean interval from onset to diagnosis fell only slightly, from 7·5 to 5·2 years, indicating that a substantial number of undiagnosed cases are present in the community even after intensive observation.

Analysis of death certificates disclosed that the first certificate with the diagnosis of disseminated sclerosis appeared in 1898, but further analysis suggested that the disease may have occurred with the same frequency in the late nineteenth century as it did in the 20 years surveyed.

An increase in prevalence was observed over the period that comprised the four studies, with a remarkable 200% increase in Orkney and a much smaller increase (29%) in Shetland, which appears to be due to increasing survival (duration) of the disease. This result might be expected on clinical grounds through the prevention of pneumonia and urinary tract infections and their associated mortality. Five factors were considered as possible contributing factors to the increasing prevalence. These included: (1) an increasing incidence, which was not confirmed in this study; (2) increasing duration of the disease, which was believed to be the major contributing factor; (3) alterations in the age structure of the population, which were not significant in this study; (4) more complete case ascertainment as a result of restudy at short intervals; and (5) emigration from the islands and differential emigration of well individuals leaving behind those affected by MS.

The remarkably high incidence of MS in these islands, the increased duration of disease, and the almost complete ascertainment of cases contributed to the highest and most rapidly increasing prevalence of MS reported anywhere in the world.

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